

Peer Review File

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Reviewer A

Comment 1: *The retrospective cohort study on "Opportunities to Improve the Diagnosis and Treatment of Primary Hyperparathyroidism" delves into the underrecognition and undertreatment of this condition within a health system. With a focus on characterizing patient evaluations and treatment trends, the study sheds light on crucial areas for improvement in managing primary hyperparathyroidism (PHPT).*

The study, spanning from January 2018 to June 2023, identified a significant cohort of patients with chronic hypercalcemia. Only 43.3% of these patients underwent parathyroid hormone (PTH) testing within six months, highlighting a substantial gap in PHPT evaluation. Factors such as age, calcium levels, and osteoporosis emerged as significant influencers in the likelihood of PHPT evaluation, suggesting avenues for targeted intervention and education among healthcare providers.

Among patients with biochemical evidence of PHPT, a concerning 39.9% went unrecognized, indicative of diagnostic shortcomings within the healthcare system.

Furthermore, only 26% of patients with PHPT received definitive treatment through parathyroidectomy, despite its potential to provide a cure with low-risk surgery. The study underscores missed opportunities in recognizing and appropriately managing PHPT, emphasizing the need for proactive measures to bridge this gap.

Overall, the study underscores the pressing need for enhanced awareness, screening, and management protocols for PHPT within healthcare systems. By identifying key areas for improvement, such as increasing rates of PHPT evaluation and optimizing treatment pathways, the study paves the way for targeted interventions to enhance patient outcomes and reduce the burden of untreated PHPT.

Reply 1: We thank the Reviewer for taking the time to review our work.

Changes in the text: None needed.

Reviewer B

Comment 1: *Please be more descriptive in terms of how secondary hyperparathyroidism was ruled out. As part of this, please describe if the evaluation of Vitamin D levels went into making this determination, or 24 hour urine calcium, or both*

Reply 1: We thank the Reviewer for this comment. We relied on ICD-10 codes only to exclude patients with secondary hyperparathyroidism.

Changes in the text: On page 7, we have inserted the line: “Specifically, laboratory values were not used to identify and exclude patients with secondary or tertiary hyperparathyroidism.”

Comment 2: *Please also comment on whether med list containing biotin, which is known to falsely lower PTH, was part of the evaluation. It seems unlikely based on the described methods but if not this should be added to the discussion as an unmeasured potential confounder*

Reply 2: We did not consider biotin as an interfering medication. Biotin is a frequent additive to multivitamins and supplements in the United States, and these supplements are not reliably tracked within the medical record. Thank you for bringing this to our attention.

Changes in the text: We now add the following into the Limitations section of the Discussion: “Fourth, we did not consider whether patients were taking biotin, which can lead to falsely low PTH levels. While this may decrease the proportion of patients with PHPT in this study, the consideration of biotin does not alter the appropriate evaluation of hypercalcemia by obtaining a PTH test.”

Reviewer C

Comment 1: *The submitted manuscript regarding clinical practice of hypercalcemia is interesting and well designed and written.*

There are some issues to address.

Reply 1: We thank the Reviewer for taking the time to improve our work.

Changes in the text: None needed.

Comment 2: *Abstract: In conclusion, try to avoid exact numbers.*

Reply 2: We have made changes to the Abstract.

Changes in the text: We have revised the sentence to now read: "Among patients with biochemical evidence of PHPT, one-third were unrecognized and only one-in-four received curative treatment."

Comment 3: *Text:*

Results, Line 17-21: sentence is not clear, please rephrase. Same for next sentence (Line 22-26)

Reply 3: We have attempted to clarify these sentences.

Changes in the text: We now write: "We examined seven indications for surgery as shown in Table 1: age <50 years, kidney stones, osteoporosis, pathologic bone fracture, serum total calcium >1 mg/dL above normal, eGFR <60 mL/min/1.73 m² and hypercalciuria. Patients with PTH tests, compared to without, were less often younger than 50 years of age (10.4% vs. 15.9%, $p<0.001$) and more often had kidney stones (11.0% vs. 7.9%, $p<0.001$). Patients with PTH tests also more often had osteoporosis (41.4% vs. 20.8%, $p<0.001$), pathologic bone fractures (6.9% vs. 4.4%, $p<0.001$), and serum total calcium levels >1 mg/dL above normal (36.8% vs. 20.1%, $p<0.001$) as compared to those without PTH tests.

On multivariable analysis, patients were more likely to have PTH tests if they were between 40-49 years of age versus <30 years (odds ratio [OR] 3.2, 95% confidence interval [CI] 1.8-5.6, $p<0.001$), if they had a serum calcium level between 11.6-12.0 mg/dL versus <11.0 mg/dL (OR 3.9, 95% CI 3.2-4.7, $p<0.001$), and if they had osteoporosis (OR 3.1, 95% CI 2.7-3.5, $p<0.001$) (Table 2).

Comment 3: *Line 34-35: is there overlapping in those numbers? i.e. some patients had evaluations by an endocrinologist, surgeon or parathyroidectomy? It is not clear.*

Reply 3: Thank you for this comment. These counts are not mutually exclusive to each category, and we have used the percentages to designate this. Indeed, a patient did not need to see an Endocrinologist to see a surgeon or vice versa. We have attempted to clarify further.

Changes in the text: We have added a line, which reads: “Counts are not mutually exclusive among these three categories.”

Comment 4: *What is the explanation for the low percent of PTX in patients with bone fractures and PHPT? Are all those bone fractures pathological?*

Reply 4: It is possible that patients with pathologic bone fractures are elderly and frail, thus carry too high of a surgical risk to undergo parathyroidectomy. Within the limitations of administrative data, all bone fractures identified in our study are pathological.

Changes in the text: None needed.

Reviewer D

Comment 1: *Very interesting article, it correlates to clinical experience. When we analyze laboratory records of patients referred to surgery by endocrinologists, lots of them had hypercalcemia since 2 or 3 years prior to indication of surgery.*

Reply 1: We thank the Reviewer for taking the time to improve our work. We also observe patients this considerable chronic hypercalcemia in our patients. It is clearly a worldwide problem that needs to be addressed.

Changes in the text: None needed.

Comment 2: *1. I would recommend to authors discuss more about time range (2018 to 2023), since COVID epidemic might have played a hole in delaying medical assistance.*

Reply 2: Thank you for this comment. We have added a line to the Limitations section of the Discussion.

Changes in the text: We have added a line, which reads: "Our study period overlapped with that of the COVID-19 pandemic, which may have also underestimated our results."

Comment 3: *2. I would like to hear your thoughts on other reasons why clinicians might delay to investigate or to refer patients with PHPT to surgery. We have impression that negative or inconclusive "localizatory" tests (ultrasound/ Sestamibi cintigraphy or 4D CT scan) maybe missincourage clinicians to consider surgical treatment*

Reply 3: We also believe this to be the case anecdotally as Endocrinologists may not refer for surgical consultation unless a parathyroid adenoma can be visualized on imaging. However, it is important to remember, as the Reviewer knows well, that PHPT is a biochemical diagnosis and the recommendation to pursue surgical treatment is based upon the biochemical diagnosis only, and not findings on imaging. Imaging is used to facilitate a focused parathyroidectomy. Qualitative research to understand the decision-making behind when an Endocrinologist refers a patient for surgical consultation is needed to better delineate the reasons for such delays. Thank you for sharing your experiences.

Comment 4: *3. Another topic on discussion would be the financial impact to Healthcare of broader PTH testing in chronic hypercalcemia, considering the cost of testing in USA and if there is any cost-effective analysis in literature.*

Reply 4: There are no direct studies in the US examining the cost-effectiveness of PTH testing in chronic hypercalcemia. We provided a paragraph discussing financial implications of PHPT.

Changes in the text: None needed